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Clinical paper

Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest☆

John Bro-Jeppesen[a,*], Christian Hassager[a], Michael Wanscher[b], Helle Søholm[a], Jakob H. Thomsen[a], Freddy K. Lippert[c], Jacob E. Møller[a], Lars Køber[a], Jesper Kjaergaard[a]

[a] Department of Cardiology, The Heart Centre, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[b] Department of Cardiothoracic Anaesthesia, The Heart Centre, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[c] Emergency Medical Services, The Capital Region of Denmark, Copenhagen, Denmark

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ABSTRACT

Objective: Post-cardiac arrest fever has been associated with adverse outcome before implementation of therapeutic hypothermia (TH), however the prognostic implications of post-hypothermia fever (PHF) in the era of modern post-resuscitation care including TH has not been thoroughly investigated.

The aim of the study was to assess the prognostic implication of PHF in a large consecutive cohort of comatose survivors after out-of-hospital cardiac arrest (OHCA) treated with TH.

Methods: In the period 2004–2010, a total of 270 patients resuscitated after OHCA and surviving a 24-h protocol of TH with a target temperature of 32–34 °C were included. The population was stratified in two groups by median peak temperature (≥38.5 °C) within 36 h after rewarming: PHF and no-PHF. Primary endpoint was 30-days mortality and secondary endpoint was neurological outcome assessed by Cerebral Performance Category (CPC) at hospital discharge.

Results: PHF (≥38.5 °C) was associated with a 36% 30-days mortality rate compared to 22% in patients without PHF, $p_{\text{log-rank}} = 0.02$, corresponding to an adjusted hazard rate (HR) of 1.8 (95% CI: 1.1–2.7), $p = 0.02$). The maximum temperature (HR = 2.0 per °C above 36.5 °C (95% CI: 1.4–3.0), $p = 0.0005$) and the duration of PHF (HR = 1.6 per 8 h (95% CI: 1.3–2.0), $p < 0.0001$) were also independent predictors of 30-days mortality in multivariable models. Good neurological outcome (CPC1-2) versus unfavourable outcome (CPC3-5) at hospital discharge was found in 61% vs. 39% in the PHF group compared to 75% vs. 25% in the No PHF group, $p = 0.02$.

Conclusions: Post-hypothermia fever ≥38.5 °C is associated with increased 30-days mortality, even after controlling for potential confounding factors. Avoidance of PHF as a therapeutic target should be evaluated in prospective randomized trials.

1. Introduction

Therapeutic hypothermia (TH) plays a central role in post-resuscitation care after out-of-hospital cardiac arrest (OHCA) and is recommended in patients remaining comatose after return of spontaneous circulation (ROSC).[1] TH is induced to attenuate neurological injuries and may act through a variety of mechanisms; e.g. inhibition of apoptosis, reducing cerebral metabolism and oxidative stress, which may all contribute to the beneficial effects of TH.[2,3] A recent Cochrane review evaluated TH as a strategy to improve outcome after OHCA and suggested that the neuroprotective effects of TH may at least partly be due to an antipyretic effect.[4] Development of fever is most frequently an adaptive response to cell damage, activation of inflammatory cascades or infections.[5] Development of fever after cardiac arrest is frequent and has previously been found to be associated with unfavourable outcome.[6–8] However, these studies reported fever as a prognostic marker in relatively small series of cardiac arrest patients before implementation of TH. Prior studies regarding prognostic implications of post-cardiac arrest fever in patients treated with TH are thus limited and the findings have been ambiguous.[9,10]

This study reports a tertiary single centre experience on the association between post-hypothermia fever (PHF) and outcome in consecutive comatose survivors of OHCA admitted for post-resuscitation care with TH.

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2013.07.023.

* Corresponding author at: Department of Cardiology 2142, The Heart Centre, Copenhagen University Hospital Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
E-mail address: jbj@dadlnet.dk (J. Bro-Jeppesen).

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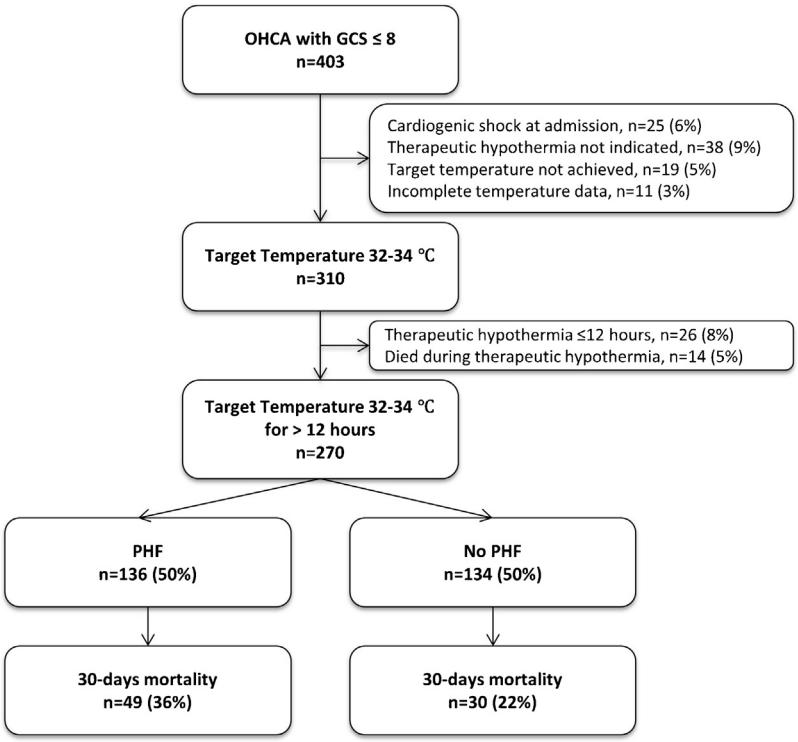

Fig. 1. Flow chart. This figure shows included and excluded patients admitted to Copenhagen University Hospital Rigshospitalet after OHCA in the period 2004–2010. GCS, Glascow Coma Scale; OHCA, Out-of-Hospital Cardiac Arrest; PHF, Post-hypothermia fever.

2. Methods

2.1. Setting and study population

We performed a prospective observational cohort study enrolling consecutive comatose patients resuscitated from OHCA and admitted to the Copenhagen University Hospital Rigshospitalet in the period 1st June 2004 to 31th October 2010.

The physician staffed mobile emergency care unit covers the central Copenhagen with approximately 600,000 resident inhabitants increasing during daytime by 20% and the greater area of Copenhagen (population 1,200,000). Patients suffering OHCA are referred to the nearest available hospital after ROSC. Patients suffering from OHCA in the central Copenhagen area were admitted for post-resuscitation care at Rigshospitalet. In addition, patients resuscitated from OHCA in the greater Copenhagen area are transferred for emergency percutaneous coronary intervention in case of suspected coronary occlusion.

Inclusion criteria were (1) OHCA with presumed cardiac aetiology; (2) age $\geq$ 18 years; (3) sustained ROSC >20 min; (4) Glasgow Coma Scale (GCS) $\leq$8 upon arrival in the emergency department or cardiac intensive care unit (ICU).

Patients were excluded if cardiogenic shock was present at time of admission to ICU according to definitions in the SHOCK-trial.[11] Patients were excluded if hypothermia treatment was not indicated, if target temperature (<34 °C) was not achieved or if rewarming was initiated less than 12 h of achieving target temperature in case of haemodynamic instability. In addition, patients not surviving until the rewarming phase of TH and thus never reached a core temperature greater than 36.5 °C were excluded from the analysis, Fig. 1.

2.2. Post-cardiac arrest care

All patients were admitted to the cardiac ICU for post-resuscitation care and treated according to a goal directed protocol for optimizing haemodynamic and metabolic parameters. General treatment goals were mean arterial pressure above 65 mmHg, heart rate of 40–90 min^{-1}, central venous pressure of 10–15 mmHg and diuresis >1.5 mL/kg/h. An initial neurological examination was performed upon arrival at the emergency department or the ICU assessing level of consciousness and if GCS $\leq$ 8, TH was administered according to guidelines as soon as possible.[12] TH was induced by infusion of 30 mL/kg of 4 °C Ringer's solution and surface cooling was applied in the ICU using an external cooling system (Allon Thermowrap™, MTRE, Israel or Emcools Flex.Pad™, Austria). All patients were treated with prophylactic intravenous antibiotic, cefuroxime 1.5 g three times a day (TID). If signs of aspiration pneumonia were present antibiotic treatment was changed to meropenem 1 g TID and metronidazole 500 mg TID. The duration of TH was defined as hours with a core temperature below 34.0 °C and was maintained for 24 h with a target temperature of 33 °C with subsequent active rewarming by 0.5 °C per hour until normothermia (36.5 °C). Treatment of PHF in the post-hypothermia period with active cooling devices was not part of the standard treatment protocol. Acute coronary angiography and PCI, if indicated was performed in all patients with ST-segment elevation pattern on ECG.

2.3. Data collection

Pre-hospital data regarding the cardiac arrest including initial arrhythmia, witnessed arrest, administration of bystander cardiopulmonary resuscitation (CPR) and time to ROSC were systematically collected upon admission according to Utstein guidelines.[13] Admission temperature was defined as the first